UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/594,825	08/22/2008	Douglas C. Wallace	UCIVN-061US	3649

33197 7590 04/21/2011

STOUT, UXA, BUYAN & MULLINS LLP
4 VENTURE, SUITE 300
IRVINE, CA 92618

EXAMINER	
GOLDBERG, JEANINE ANNE	

ART UNIT	PAPER NUMBER
1634	

MAIL DATE	DELIVERY MODE
04/21/2011	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/594,825	WALLACE ET AL.	
	Examiner	Art Unit	
	JEANINE A. GOLDBERG	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *February 22, 2011*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4 and 6-30* is/are pending in the application.

4a) Of the above claim(s) *7-12 and 22-30* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6 and 13-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to the papers filed June 21, 2010. Currently, claims 1-4, 6-30 are pending. Claims 7-12, 22-30 have been withdrawn as drawn to non-elected subject matter.

2. All arguments have been thoroughly reviewed but are deemed non-persuasive for the reasons which follow. This action is made FINAL.

3. Any objections and rejections not reiterated below are hereby withdrawn.

Election/Restrictions

4. Applicant's election without traverse of the species of T4141G Mutation and Alzheimer 's disease, Claims 6 and 21 in the paper filed June 21, 2010 is acknowledged.

In a telephone interview on August 17, 2010, the Examiner called Robert Buyan to request clarification regarding the T4141G mutation. The specification and the art teach a T414G mutation. In the telephone interview Mr. Buyan requested the examiner treat the election as T414G rather than T4141G. Moreover, **Mr. Buyan indicated he would file an amendment to this effect in response to the office action.** Therefore, in an effort to facilitate compact prosecution, an action on T414G has been prepared.

Claims 7-12, and 22-30 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

The requirement is still deemed proper and is therefore made FINAL.

Priority

5. This application claims priority as a 371 to PCT/US05/10266, filed March 29, 2005 and provisional application 60/557,612, filed March 29, 2004.

Drawings

6. The drawings are acceptable.

Claim Rejections - 35 USC § 112-Scope of Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-4, 6, 13-21 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for determining the presence of mtDNA CR mutations, does not reasonably provide enablement for a method for diagnosis of any disorder associated with the development of beta amyloid deposits or fibrils, such as Alzheimer's disease, in a human or animal by determining the presence or quantity of mtDNA CR mutations, such as T414G. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and breadth of claims

The claims are drawn to methods for diagnosis of any disorder associated with the development of beta amyloid deposits or fibrils, such as Alzheimer's disease, in a human or animal by determining, by quantifying, the presence or quantity of mtDNA CR mutations, such as T414G and comparing a mtDNA value to a mtDNA value representative of subjects who suffer from a disorder associated with the development of beta amyloid deposits or fibrils.

Claims to diagnosis require a reliable association between the genotype and the phenotype.

The invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The unpredictability of the art and the state of the prior art

The art teaches the detection of mtDNA control region mutations as a diagnostic for disorders associated with the development of beta amyloid deposits or fibrils in a human or animal is unpredictable at the time the invention was made.

Murdock et al. (Nucleic Acids Research, Vol. 28, No. 21, pages 4350-4355, 2000) teaches age-related accumulation of the T414G mitochondrial DNA control region mutation in muscle, but not in brain. Murdock analyzes the mtDNA using a sensitive PNA-directed PCR clamping based method. In particular the T414G mtDNA mutation was analyzed in both human skeletal muscle and brain samples for the accumulation of the mutation with age (page 4351, col. 1). The relative quantities of mtDNA were measured using competitive PCR (page 4351, col. 2). As seen in Figure 2, PNA-clamping blocks wild-type, but not mutant, molecule amplification to prevent false positive amplification (page 4352, col. 1). To increase the sensitivity of the PNA-clamped reaction, a second round of PCR on diluted product from the first reaction may be performed using restriction enzyme digestion (page 4352, col. 2-4353, col. 1). Murdock concludes that PNA-clamped reactions can be multiplexed to allow simple and efficient identification of multiple mtDNA mutation in diagnosis of mtDNA disease (page 4351, col. 2). The PNA-clamping also permits low levels of heteroplasmy mutations to be detected at a ratio of 1:100. Thus, the control region mtDNA mutation T414G was found in skin fibroblasts from older human subjects and also accumulates in skeletal muscle after age 35 years (page 4354, col. 1). The T414G mutation could not be detected in any human brain sample, even from subjects as old as 93 years (page 4354, col. 1).

Chinnery et al. (Am. J. Hum. Genetics, Vol. 68, pages 529-532, published electronically December 21, 2000) teaches determining the presence of mtDNA control region (CR) mutations. In particular Chinnery studied the mtDNA control region in brain

tissue from 31 normal elderly individuals, from 35 individuals who had Alzheimer disease and from 47 individuals who had dementia with Lewy bodies. Chinnery teaches postmortem control brain tissue was collected. Chinnery teaches sequencing nucleotides 33-785 of the control region which included the T414G mutation using primer extension reactions and electrophoresis (page 530, col. 1-2). Chinnery fails to detect the T414G polymorphism in any of the 113 samples of brain DNA, either control or individuals with AD. It is unpredictable how the skilled artisan would diagnose AD based upon the T414G polymorphism.

Simon et al. (Genomics, Vol. 73, pages 113-116, 2001) teaches screening for the T414G mutation in brain-derived mtDNA from 8 Alzheimer's disease patients, 27 Parkinson's disease patients, 4 multiple system atrophy patients and 44 controls. Simon failed to detect the T414G mutation in any of the cases (abstract). Simon teaches sampling brain samples from 4 different regions of the brain (page 114, col. 2). Simon also analyzed blood and fibroblasts and the T414G mutation was absent from these tissues also. Simon suggests that there is a possibility that the T414G mutation may be present in brain regions not examined in their study (page 115, col. 1).

Coskun et al. (PNAS, Vol. 101, No. 29, pages 10726-10731, July 20, 2004), applicant's own work, finds that 65% of the AD brains harbored the T414G mutation whereas this mutation was absent from all controls (abstract). Coskun acknowledges the T414G mutation was not detected by others using less sensitive primer extension strategies such as Chinnery.

Howell (Trends in Genetics, Vol. 21, No. 11, pages 583-586, November 2005) considers previous studies performed by Chinnery and Coskun and concludes that the role of mtDNA mutations in the development of AD or PD still remains unestablished (abstract). When considering the results by Coskun, Howell states that the new results

of Coskun are inconsistent with previous findings. Howell suggests that the study by Chinnery involved larger number of tissue samples and did not detect the mutation in brains, AD patients or those with dementia and Lewy bodies. Howell suggests the inconsistent findings may be due to different samples of brain tissue. Howell also considers the findings of higher levels of mutations which were not observed by Chinnery. Howell further considers the scientific concerns that mtDNA point mutations are random and independent, how a heteroplasmic somatic mtDNA mutation can reach high levels in the brain tissue of these patients. Howell states that purely on statistical grounds the chances of an mtDNA mutation arising early in the cell lineage that gives rise to the brain will be extremely low. Howell states it is difficult to envisage such a chance event occurring often enough in the human population to account for the prevalence of AD (page 584, col. 2).

Guidance in the Specification.

The specification teaches amyloid fibrils are thought to be involved in the pathogenesis of various amyloid diseases of genetic, infectious and/or spontaneous origin including Alzheimer's disease, spongiform encephalopathies, Parkinson's disease, type II diabetes, Creutzfeldt-Jakob disease, Down's syndrome associated dementia, Huntington's disease, macular degeneration various prion diseases and numerous others. This is a very diverse collection of diseases.

The specification teaches that the mtDNA control region (CR) is a 1000 nucleotide pair, non-coding, region of the mtDNA that contains the promoters for the initiation of heavy (H) and L-strand transcription (PH & PL) (page 2 of the specification). The mtDNA CR encompasses the light (L) - and heavy (H) strand promoters (Pl and Ph), mtTFA, CSB I, II, and II, Oh1 and Oh2 (page 2 of the specification).

The specification analyzes the total number of heteroplasmic mtDNA CR mutations observed by cloning and sequencing CR clones from AD and control brain samples (page 5, lines 7-10). Figure 3A illustrates the differences between AD and control brains to demonstrate a significant difference. Figure 3B illustrates the difference in patients 80 years and up is significant.

With respect to analysis of the T414G mutation, Example 1 tests for the mutation by PNA clamping PCR in AD brain frontal cortex (page 6 of the specification). The specification sampled a total of 23 AD and 40 control (non-AD) brains (page 9 of the specification). The mutation was found in 65% of the AD brains while none of the normal control brains had the mutation.

The guidance provided by the specification amounts to an invitation for the skilled artisan to try and follow the disclosed instructions to make and use the claimed invention.

Quantity of Experimentation

The quantity of experimentation in this area is extremely large since there is significant number of parameters which would have to be studied to enable the skilled artisan to practice the claimed invention as broadly as claimed.

First the claims are directed to any disorder associated with the development of beta amyloid deposits or fibrils. The specification teaches the genus of disorders encompasses genetic, infectious and/or spontaneous origin including Alzheimer's disease, spongiform encephalopathies, Parkinson's disease, type II diabetes, Creutzfeldt-Jakob disease, Down's syndrome associated dementia, Huntington's disease, macular degeneration various prion diseases and numerous others (see page 2 of the specification). The art teaches the CR mutations are not associated with Lewy

bodies and dementia (see Chinnery, 2000). There is no evidence that diabetes type II patients have any CR mutations at a statistically significant level. The instant specification fails to provide any evidence that all of these disorders are predictably associated with CR mutations. It is unpredictable that each of these distinct disorders is similarly associated with CR mutations absent further unpredictable and undue experimentation.

Second, the claims are directed to both humans and animals. The specification and the art appear to be focused on humans. There are no teachings in the art or the specification whether animals may be diagnosed with disorders associated with the development of beta amyloid deposits or fibrils based upon mtDNA CR mutations. It is unpredictable which mutations, if any mutations are present in animals such as dogs, cat, chimps, rabbits, for example. It is further unpredictable whether these animals accumulated mtDNA mutations in the same manner as humans. Without further, unpredictable and undue experimentation the skilled artisan would be unable to make any diagnosis for dogs, cats, rabbits, chimps regarding mtDNA CR mutations.

Third, with regard to the detection of the mtDNA CR T414G mutation, the prior art teaches the T414G mutation is found in both young and older individuals' fibroblasts (see Michikawa). Murdock teaches the T414G mutation could be detected in muscle from individuals 30 years and older. This suggests that the T414G mutation is found in normal, non diseased individuals. It would be unpredictable that the mere detection of T414G would be indicative of a disorder associated with the development of beta amyloid deposits or fibrils in humans. If the claims were limited to brain tissue samples, it is unpredictable how the skilled artisan could obtain brain tissue to be able to diagnose an individual prior to post mortem in an effective manner.

Fourth, with regard to the particularly elected embodiment of detecting T414G mutation as indicative of Alzheimer's disease, the prior art teaches a lack of association of the mutation with AD. Murdock teaches that the T414G mutation could not be detected in any human brain sample, even from subjects as old as 93 years (page 4354, col. 1). Chinnery fails to detect the T414G polymorphism in any of the 113 samples of brain DNA, either control or individuals with AD. Simon also analyzed brain-derived mtDNA for the T414G mutation from 8 Alzheimer's disease patients, 27 Parkinson's disease patients, 4 multiple system atrophy patients and 44 controls but failed to detect the T414G mutation in any of the cases. It is unpredictable how the skilled artisan would diagnose AD based upon the T414G polymorphism since the art teaches the T414G mutation is not found in brain tissue or more specifically brain tissue from AD or Parkinson's disease patients. The post-filing date art reviews that studies from Chinnery and Coskun (applicant's work) and concludes the role of mtDNA mutations in the development of either AD or PD still remains to be established. Howell expresses scientific concerns with the frequency at which Coskun detected the mtDNA mutations. In particular Howell stated that the results were inconsistent with previous findings that involved larger number of tissue samples. Howell also rationalized that "purely on statistical grounds, the chances of an mtDNA mutation arising early in the cell lineage that gives rise to the brain will be extremely low. It is difficult to envisage such a chance event occurring often enough in the human population to account for the prevalence of AD." Thus, given the inconsistent results and the scientific rationale provided by Howell, it is unpredictable that the skilled artisan could diagnose AD using the T414G mutation absent further unpredictable and undue experimentation. This would require significant inventive effort, with each of the many intervening steps, upon

effective reduction to practice, not providing any guarantee of success in the succeeding steps.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

In the instant case, as discussed above, in a highly unpredictable art where the art teaches the unpredictability of detecting mtDNA CR mutations for diagnosis disorders. Further, the prior art and the specification provides insufficient guidance to overcome the art recognized difficulties of diagnosing disorders based upon mtDNA CR mutations. Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the absence of a working example and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Response to Arguments

The response traverses the rejection. The response asserts that step B of Claim 1 is fully enabled. The response argues that the application as a whole enables the person of ordinary skill in the art to generate reference data and to compare. This argument has been considered but is not convincing because the specification and the art fail to teach a reliable correlation between the mtDNA CR value in a patient and the

mtDNA CR value representative of subjects who suffer from a disorder associated with the development of beta amyloid deposits or fibrils.

The rejection above discusses the breadth of the claims as directed to any disorder associated with the development of beta amyloid deposits or fibrils and any animal. The response filed February 22, 2011 fails to address these broad limitations and why the claimed invention is enabled over the full scope of the claims. The response focuses on Example 1 from the specification which is directed to Alzheimer's disease, one particular disorder, in humans, again one member of the genus and T414G mtDNA. This very narrow embodiment of the instant claims is not representative over the full scope of the claims.

Even though Example 1 is directed to AD, humans and T414G, the art specifically speaks to the study performed by Coskun. As noted in the rejection above, Howell considers the studies performed by Chinnery and Coskun and concludes that the role of mtDNA mutations in the development of AD or PD still remains unestablished (abstract). The response field on February 22, 2011 fails to consider the teachings in the art regarding the unpredictability of the association of T414G with AD. In particular, Howell states that the new results of Coskun are inconsistent with previous findings. Howell suggests that the study by Chinnery involved larger number of tissue samples and did not detect the mutation in brains, AD patients or those with dementia and Lewy bodies. Howell suggests the inconsistent findings may be due to different samples of brain tissue. Howell also considers the findings of higher levels of mutations which were not observed by Chinnery. Howell further considers the scientific concerns that

mtDNA point mutations are random and independent, how a heteroplasmic somatic mtDNA mutation can reach high levels in the brain tissue of these patients. Howell states that purely on statistical grounds the chances of an mtDNA mutation arising early in the cell lineage that gives rise to the brain will be extremely low. Howell states it is difficult to envisage such a chance event occurring often enough in the human population to account for the prevalence of AD (page 584, col. 2). Therefore, it is unpredictable whether the results provided in Example 1 of the specification may be reproduced in a reliable and predictable manner such that ordinary artisan would be enabled to practice the claimed invention of diagnosis of a disorder based upon the quantitative determination of mtDNA.

Thus for the reasons above and those already of record, the rejection is maintained.

New Grounds of Rejection Necessitated by Amendment

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Newly amended Claims 1-4, 6, 13-21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claim 1 has been amended to require "the quantitative determination made in Step A" however Claim 1 fails to require a quantitative determination in step A. As evidenced by Claim 2, for example, the determining the presence of mtDNA CR mutations encompasses qualitative determination. Therefore, "the quantitative determination" lacks antecedent basis. Claim 5 previously depended on Claim 3 which in turn depended on Claim 1. Claims 2-4, 6, 13-21 depend on Claim 1 and are similarly indefinite.

The following is a quotation of the fourth paragraph of 35 U.S.C. 112:

> Subject to the following paragraph, a claim in dependent form shall contain a reference to a claim previously set forth and then specify a further limitation of the subject matter claimed. A claim in dependent form shall be construed to incorporate by reference all the limitations of the claim to which it refers.

9. Newly amended Claims 2-4 are rejected under 35 U.S.C. 112, fourth paragraph, as failing to further limit Claim 1. Claim 1 has been amend to add the limitations of Claim 5. Claim5 depended on Claim 3 which in turn depended on Claim 1.

b. Claim 2 requires a qualitative determination, however Claim 1 requires a quantitative determination. Claim 2 does not further limit Claim 1, as qualitative does not further limit a quantitative determination.

c. Claim 3 requires a quantitative determination which Claim 1 already requires. Claim 3 does not provide any additional limitations.

d. Claim 4 requires analyzing a control, where as Claim 1 already requires analyzing subjects who suffer from a disorder associated with the development of beta amyloid deposits or fibrils. Claim 4 does not appear to further limit Claim 1.

Conclusion

10. No claims allowable.

11. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Wang et al. PNAS, Vol. 98, No. 7, pages 4022-4027, March 27, 2001. Wang teaches the T414G mutation was not present in muscle.

12. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (571) 272-0743. The examiner can normally be reached Monday-Friday from 7:00 a.m. to 4:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, David Nguyen, can be reached on (571)272-0731.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

The Central Fax Number for official correspondence is (571) 273-8300.

/Jeanine Goldberg/
Primary Examiner
April 19, 2011